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TITLE: Bench to Bedside: Understanding Symptom Response to Acupuncture Treatment and Designing a Successful Acupuncture Treatment Program

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14. ABSTRACT This project is a secondary data analysis and program evaluation of the Congressionally Directed Medical Research Program funded project "The Effectiveness of Acupuncture in the Treatment of Gulf War Illness" (W81 XWH). <u>Objectives:</u> This application has two objectives to complete using data from the parent grant: 1) Better define and describe this complex disease and how healing may happen using acupuncture, 2) Report on the best acupuncture protocols for GWI veterans and specific GWI presentations. Following the directives of the "Recommendation for Funding" letter of April 11, 2014, two Specific Aims from the original application are supported: Aim 2: Complete scale construction for remaining psychosocial and clinical measures, Aim 3: Determine the relationships between dose of acupuncture and effect on secondary outcomes in this sample. Toward production of manuscripts our team has continued with regular meetings (approximately every 6 weeks) with follow-up group e-mails solidify our process. We have two papers in manuscript development now: 1) <i>Baseline Characteristics of a Sample of Veterans with Gulf War Illness</i> , 2) <i>Complex Baseline Predictors of Symptom Improvement Following Acupuncture Treatment of Gulf War Illness</i> . Lastly information on real dose of treatment used for each patient has been codified and work will begin on this paper in the next.					
15. SUBJECT TERMS Gulf War Illness, Complex Medical Illness, Acupuncture, Treatment Trial, Secondary Date Analysis					
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1. INTRODUCTION:

This project is a secondary data analysis and program evaluation of the Congressionally Directed Medical Research Program funded project “The Effectiveness of Acupuncture in the Treatment of Gulf War Illness” (W81 XWH). Objectives: This application has two objectives to complete using data from the parent grant: 1) Better define and describe this complex disease and how healing may happen using acupuncture, 2) Report on the best acupuncture protocols for GWI veterans and specific GWI presentations

2. **KEYWORDS:** Gulf War Illness, Complex Medical Illness, Acupuncture, Treatment Trial, Secondary Data Analysis

3. ACCOMPLISHMENTS:

What were the major goals of the project?

Following the directives of the “Recommendation for Funding” letter of April 11, 2014, two Specific Aims from the original application are supported: **Aim 2: Complete scale construction for remaining psychosocial and clinical measures, Aim 3: Determine the relationships between dose of acupuncture and effect on secondary outcomes in this sample.** Aim 2 was completed last year (2015) as was planned in the statement of work.

What was accomplished under these goals?

As planned the team has continued with regular meetings (approximately every 6 weeks) with follow-up group e-mails solidify our process. Toward Aim 2 we have two papers in manuscript development now: 1) *Baseline Characteristics of a Sample of Veterans with Gulf War Illness*. For this paper we have collated the baseline biomedical data into tables, as well as the Chinese Medicine initial diagnoses gathered for the whole sample from subject charts. This descriptive paper may become two papers, as it may be more efficient to target the biomedical, and Chinese Medicine audiences separately. 2) *Complex Baseline Predictors of Symptom Improvement Following Acupuncture Treatment of Gulf War Illness*. In order to take advantage of the complexity of our data, while avoiding the bias of multiple comparisons, we are working with our consultant biostatistician (Joe Locascio, PhD), utilizing exploratory factor analysis, to discover how baseline measurements move together. We have found evidence of four factors; psychological/physical health, belief/expectation, health behaviors, social context. Our next step is to see how these factors may predict symptom outcomes using longitudinal regression.

Toward Aim 3, dose information from the subject charts has been tabulated and work on this manuscript will begin in November 2016.

What opportunities for training and professional development has the project provided?

Not Applicable/Nothing to Report.

How were the results disseminated to communities of interest?

Three abstracts were presented at the Society for Acupuncture Research's Annual Conference Nov 11th-13, 2015: 1. *How TCM Practitioners Treat Gulf War Illness; findings of an RCT with individualized treatments*, 2. *Improvements in Perceived Social Support and Health Behaviors following Acupuncture Treatment in a Veteran Population*, 3. *A Case Study of Gulf War Illness in a Woman*.

For this year, we have submitted abstracts to conferences that are meeting places for acupuncture practitioners and researchers from the general community as well as representatives of the Army and the Department of Veterans Affairs. Toward the next Society for Acupuncture Research meeting April 27-29, 2017 (acupunctureresearch.org), we have submitted one abstract: 1) *Development of Therapeutic Alliance in Acupuncture Treatments in a Veteran Population*. Also for April 24, 2017 we have been invited to give a scientific talk reviewing these findings and those of the parent grant at the University of California's medical campus (San Francisco campus). This latter speaker series attracts scientists in the area; in particular, the talk is being advertised to members of the Veterans Administration (VA) and collaborators.

We also submitted (and are accepted to present) an abstract (*Using Acupuncture to Treat Complex Veteran Illness*) displaying our results at the Osher Center for Integrative Medicine Network Forum in Boston MA, Nov 18th, 2016 (<http://oshercenter.org/integrative-medicine-network-forum-2016/>). In addition to a poster presentation, our project was one of only 10 chosen to be presented as an oral presentation.

We have also been invited to write a lay version of our Plos_1, parent trial paper (*The Effectiveness of Individualized Acupuncture Protocols in the Treatment of Gulf War Illness: A Pragmatic Randomized Clinical Trial*. <http://dx.plos.org/10.1371/journal.pone.0149161>) for the acupuncture trade publication ACUPUNCTURE TODAY. This product is currently being written and will inform the acupuncture community of our results. This periodical is the leading supplier of acupuncture and Chinese Medicine information in the country (<http://www.acupuncturetoday.com>).

What do you plan to do during the next reporting period to accomplish the goals?

We will continue with these projects to produce manuscripts. As well, we will continue to network with other researchers, within and outside the VA, to disseminate our results and strengthen a network of collaboration; for example, we have begun to create a network of VA clinicians and researchers who are interested in Integrative Medicine including Cathy St Pierre MD (Bedford, MA VA), Stephanie Taylor PhD (Associate Director of Health Services Research and Development, Veterans Administration), Kristen Tillisch MD (Ronald Reagan UCLA Medical Center), Dee Lane (Founder of Campaign for Military Families, Burlington MA), Christine Cronin DAOM (Faculty member Pacific College of Oriental Medicine and Clinic Supervisor at the Veterans Free Clinic, American Legion Post #731).

4. IMPACT:

What was the impact on the development of the principal discipline(s) of the project?

Nothing to Report

What was the impact on other disciplines?

Nothing to Report

What was the impact on technology transfer?

The results of this project will allow for a smooth implementation of an acupuncture treatment program for veterans, active military personnel, and the general citizen. This information will be most easily applied by, and results will be supplied to, the Department of Veterans Affairs.

What was the impact on society beyond science and technology?

Our results have the potential to inform medical decision making in support of acupuncture as a viable treatment for veterans with GWI.

5. CHANGES/PROBLEMS

Nothing to Report

6. PRODUCTS:

Publications, conference papers, and presentations

Three abstracts were presented at the Society for Acupuncture Research's Annual Conference Nov 11th-13, 2015. 1. *How TCM Practitioners Treat Gulf War Illness; findings of an RCT with individualized treatments*, 2. *Improvements in Perceived Social Support and Health Behaviors following Acupuncture Treatment in a Veteran Population*, 3. *A Case Study of Gulf War Illness in a Woman*.

Journal publications

The results of the parent trial were published in Plos_1

(<http://dx.plos.org/10.1371/journal.pone.0149161>): *The Effectiveness of Individualized Acupuncture Protocols in the Treatment of Gulf War Illness: A Pragmatic Randomized Clinical Trial*.

In addition to the manuscripts listed above, we are also working on a manuscript describing our successful recruitment and subject adherence strategies for the journal CLINICAL TRIALS. We are excited to share our processes here as the published literature suggests that GWI is difficult to recruit for, and subjects are often challenged to adhere for lengthy behavioral trials (ours was a 6 month-treatment trial).

Books or other non-periodical, one-time publications.

Nothing to Report

Other publications, conference papers, and presentations.

An overview of our Army work to date (on grants 1. *The Effectiveness of Acupuncture in the Treatment of Gulf War Illness* (W81XWH-09-2-0064), 2. *Bench to Bedside: Understanding Symptom Response to Acupuncture Treatment and Designing a Successful Acupuncture Treatment Program* (W81XWH-14-1-0533), 3. *Designing a Successful Acupuncture Treatment Program for Gulf War Illness* (W81XWH-15-1-0695) was presented at the Massachusetts College of Pharmacy and Health Sciences (MCPHS) FACULTY FORUM (May 3, 2016) and received the only award given for science. Opportunities to network such as this have led to Dr.

Conboy now serving on two veteran health committees inside the MCPHS community; positions which will facilitate future collaborations.

Website(s) or other Internet site(s)

The publication of our parent grant project results *The Effectiveness of Individualized Acupuncture Protocols in the Treatment of Gulf War Illness*, which was published in Plos_1 (<http://dx.plos.org/10.1371/journal.pone.0149161>) was highlighted on the Gulf War Illness specific WEB site, 91 Outcomes (www.91outcomes.com) on April 12, 2016. In addition, 91 Outcomes referenced our work, through the CDMRP Website, as part of the GWI Researcher Resource Initiative (October 21, 2016).

Technologies or techniques

Nothing to Report

Inventions, patent applications, and/or licenses

Nothing to Report

Other Products

Nothing to Report

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Name:	Lisa Conboy
Project Role:	Principal Investigator
Researcher Identifier:	ORCID # 0000-0003-2218-7841
Nearest person month worked:	5

Contribution to Project: Dr. Lisa Conboy has acted as the Principal Investigator on this project. She is the main statistician, completing data cleaning and scale construction of the biomedical survey data. Dr. Conboy has conducted regular meeting with consultants, co-investigator and research assistants on the project.

Funding Support: N/A

Name:	Kai-Yin Hsu
Project Role:	Research Assistant
Researcher Identifier:	ORCID # 0000-0002-5062-9953
Nearest person month worked:	6

Contribution to Project: Kai-Yin Hsu is the Research Assistant for this project. She has coded and organized acupuncture specific data. She has participated in regular meetings with her PI and consultants.

Funding Support: N/A

Name:	Dr. Joseph Locascio
Project Role:	Biostatistician
Researcher Identifier:	N/A
Nearest person month worked:	1

Contribution to Project: Dr. Joseph Locascio is the Biostatistician for the project. He has provided statistical consultation and analysis for the project.

Funding Support: N/A

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

Nothing to Report

What other organizations were involved as partners?

Dr. Joe Locasio (consultant statistician) is faculty at Massachusetts General Hospital in Boston, MA.

8. SPECIAL REPORTING REQUIREMENTS

Not Applicable

9. APPENDICES

Parent project results published in Plos_1 (<http://dx.plos.org/10.1371/journal.pone.0149161>)

Three posters presented at Society for Acupuncture Research 2015

1. *How TCM Practitioners Treat Gulf War Illness; findings of an RCT with individualized treatments*
2. *A Case Study of Gulf War Illness in a Woman*
3. *Improvements in Perceived Social Support and Health Behaviors following Acupuncture Treatment in a Veteran Population*

Abstract to be presented at Harvard Medical School/Osher Forum

Using Acupuncture to Treat Complex Veteran Illness

Abstract to be presented at Society for Acupuncture Research 2017

Development of Therapeutic Alliance in Acupuncture Treatments in a Veteran Population

How TCM Practitioners Treat Gulf War Illness; findings of an RCT with individualized treatments.

Joe Chang LicAc, Lisa Taylor-Swanson Lic Ac, Rosa Schnyer DAOM, Lisa Conboy MA MS ScD.

Purpose:

This project describes the presentations and treatment of Gulf War Illness (GWI) from a TCM point of view using various retrospective analysis techniques. Parent data comes from a completed 3.5-year Army-funded RCT “The Effectiveness of Acupuncture in the Treatment of GWI”. Individualized acupuncture treatments were administered by practitioners in the community for a possible treatment window of 6 months. A standardized treatment protocol was not used; instead experienced practitioners were given training in the known medical information of GWI, and encouraged to treat with discretion while keeping detailed treatment records. We found positive results using our biomedical outcome measurements and now turn to better understand what took place during the individual diagnosis and treatment plans. Our naturalistic data, is heterogeneous and complex representing the work of 32 practitioners treating the range of GWI presentations in the best manner they know, with only limited restriction (e.g. herbs were not allowed).

Methods: First, to better understand how patient presentations change over time, we map (using a sample of patients) each symptom using Matrix Analysis to visually explore the relationships between symptoms and diagnoses offered at baseline with those gathered over the course of treatment. Second, we use cluster analysis to empirically look for linkages between factors presented at baseline (signs, symptoms, diagnosis) to begin to articulate how to talk about GWI in terms of TCM. Our eventual project goal is to add treatment data and develop a TCM model (or models) for GWI.

Results: We are currently implementing these descriptive analyses.

Conclusion: GWI is not a recognized TCM diagnosis but the novelty of our emergent treatment data may offer new answers to difficult treatment questions. We are consolidating our clinical data into a form that practitioners can use to improve the health of GWI veterans and others with similar complex illnesses.

A Case Study of Gulf War Illness in a Woman

Lisa Taylor-Swanson Lic Ac, Lisa Conboy MA MS ScD

Background Gulf War Illness (GWI) is a complex illness with multiple symptoms, including fatigue, sleep and mood disturbances, cognitive dysfunction and musculoskeletal pain. Symptoms are often severe in intensity and interfere with activities of daily life. People with GWI experience comorbid medical diagnoses, including chronic fatigue syndrome, fibromyalgia, irritable bowel syndrome, arthralgia, depression, and anxiety disorders. GWI has not been found to create a unique syndrome by sex (Shapiro, Lasarev, & McCauley, 2002); however, there is evidence of differential endocrine change by sex (Craddock et al., 2014). Little research has evaluated women's experiences of GWI; therefore, the purpose of this study is to evaluate one woman's symptoms and change over time during the course of receiving bi-weekly acupuncture care.

Methods One female participant's chart notes were randomly selected. Thematic content analysis was employed to determine themes in symptoms and change over the course of 17 acupuncture treatments.

Results This woman experienced at the first office call: back pain (main complaint), abdominal pain, depression, anxiety, temperature dysregulation, poor sleep, irregular menses, thirst, headache, fatigue, recurrent urinary tract infections, restless leg syndrome and floaters in her vision. Her differential diagnosis was KD Qi deficiency and LIV Qi stagnation. Over the course of treatment, her back pain was decreased and sleep, mood, memory and concentration improved. However, she had not had a menstrual period in seven months. Her differential diagnosis was relatively stable over the course of treatment, except the addition of HT, LIV and KD Yin deficiency, and LIV Yang rising.

Conclusions Multiple systems are affected by GWI and biweekly treatment with acupuncture decreased several symptoms in this case. However, persistent endocrine dysregulation, evidenced by amenorrhea, indicates that ongoing acupuncture care might be beneficial. Ongoing imbalances of Yin, Yang and Qi indicate the level of severity of dysregulation in GWI.

Improvements in Perceived Social Support and Health Behaviors following Acupuncture Treatment in a Veteran Population

Lisa Conboy MA MS ScD and Christine Cronin DAOM

Purpose: There is a growing body of evidence that acupuncture treatment is effective and well tolerated by a veteran population. Less is known about the stage of reintegration a time at which the service member can face social, psychological and physical challenges¹. Social support is a known predictor of health status and correlate of health improvement. Scientific attempts to administer social support have shown at best moderate effectiveness². This analysis considers if acupuncture treatment is associated with improvements in social support and healthy behaviors in a veteran sample.

Statistics of CAM use within military populations ranges from 23% to 81.5% depending on the population surveyed and the types of CAM surveyed¹⁻⁹. Despite its varied use among veterans and military populations, 69 % of active military reported they would use CAM if it was provided in a military treatment facility (MTF) between 69%² and 73% to 99.5% of veterans would utilize CAM modalities it offered within the VA healthcare system^{3,5}.

A 2002 study involving CAM use in military veterans found that 49.6% (252 of the 508 subjects surveyed) reported CAM use and that were that military veterans who use/d CAM were significantly less likely to drink more than 2 alcoholic beverages/day and were less likely to be current smokers¹.

In 2013, our study team competed the Army funded project “The Effectiveness of Acupuncture in the Treatment of Gulf War Illness” (W81XWH-09-2-0064). This Phase II Randomized Controlled Trial (n=104) tested the effects of individualized acupuncture treatments offered in extant acupuncture practices. Statistically and clinically significant improvements were found after 6 months of treatment for our primary outcome analysis the SF-36 physical component scale score (SF-36P), as well as pain, and self-reported main complain. Measurement of Perceived Social Support as well as health behaviors were also recorded at baseline, 2, 4 and 6 months using validated reliable surveys.

Methods:

Results: Statistically significant (to $p \leq 0.05$) improvements were found in subjects perceived social support³ post program. Interestingly these affective changes were not due to the addition of new social contacts as we found no statistically significant changes in social networks⁴. The improvements appear to be due to changes in how the individuals feel in relation to their social world. Subjects also reported decreases in alcohol and tobacco use.

Conclusion: Acupuncture treatment may help veterans engage in positive health behaviors and feel more supported in their social world, and this increased support is associated with a broad range of positive mental and physical health effects. Such changes can help with re-integration to civilian life.

Harvard Medical School/Osher Forum Abstract Using Acupuncture to Treat Complex Veteran Illness

Authors: Joe Chang LicAc, Lisa Taylor-Swanson Lic Ac, Rosa Schnyer DAOM, Lisa Conboy MA MS ScD.

Purpose:

This project describes the presentations and treatment of Gulf War Illness (GWI) from a TCM point of view using various retrospective analysis techniques. Parent data comes from a completed 3.5-year Army-funded RCT “The Effectiveness of Acupuncture in the Treatment of GWI”. Individualized acupuncture treatments were administered by practitioners in the community for a possible treatment window of 6 months. A standardized treatment protocol was not used; instead experienced practitioners were given training in the known medical information of GWI, and encouraged to treat with discretion while keeping detailed treatment records. We found positive results using our biomedical outcome measurements and now turn to better understand what took place during the individual diagnosis and treatment plans. Our naturalistic data, is heterogeneous and complex representing the work of 32 practitioners treating the range of GWI presentations in the best manner they know, with only limited restriction (e.g. herbs were not allowed).

Methods: First, to better understand how patient presentations change over time, we map (using a sample of patients) each symptom using Matrix Analysis to visually explore the relationships between symptoms and diagnoses offered at baseline with those gathered over the course of treatment. Second, we use cluster analysis to empirically look for linkages between factors presented at baseline (signs, symptoms, diagnosis) to begin to articulate how to talk about GWI in terms of TCM. Our eventual project goal is to add treatment data and develop a TCM model (or models) for GWI.

Results: We are currently implementing these descriptive analyses. Results will be discussed in the context of our labs’ other GWI projects.

Conclusion: GWI is not a recognized TCM diagnosis but the novelty of our emergent treatment data may offer new answers to difficult treatment questions. We are consolidating our clinical data into a form that practitioners can use to improve the health of GWI veterans and others with similar complex illnesses.

Society for Acupuncture Research Abstract
Development of Therapeutic Alliance in Acupuncture Treatments in a Veteran Population

Authors: Saadat Bagherigaleh, MD, Lisa Conboy MA MS ScD

Purpose:

While it is well accepted in psychotherapy that Therapeutic Alliance (TA) is vital to treatment effectiveness, less has been studied about TA in other health fields such as Acupuncture. TA is purported to create the necessary climate and conditions in which other intervention contents can be successfully delivered by the therapist and absorbed by the patient. Some research also suggests that more patient-practitioner agreement on the quality of the patient-provider relationship, termed concordance, is related to better clinical outcomes.

In 2013, our study team completed a Phase II Randomized Controlled Trial (n=104) testing the effects of individualized acupuncture treatments offered in extant acupuncture practices. In addition to measuring physical and psychological symptoms we also included measures of study experience including TA, collecting both patient and practitioner experiences at multiple points in time during the study.

Methods:

Horvath's Working Alliance Inventory (WAI) was used to measure TA. The WAI contains 36 items, with three subscales (Task, Goal, and Bond). Each item is scored on a 7-point scale ranging from 1 (never) to 7 (always). The WAI has strong published support for reliability and validity. The WAI was administered to both subjects and clinicians at baseline, 2, 4, and 6 months of study exposure.

Average WAI scores were calculated for each participant and practitioner and results for each factor were graphed by patient-practitioner dyad over time. Linear regression models are used to measure the influence of degree of concordance on the outcomes of pain and physical function.

Results:

Over time, dyads reported increasingly positive scores on the WAI as the study progressed, and dyads moved toward higher levels of concordance. Regression analysis suggest that concordance across subscales results in improved outcomes.

Conclusion: These findings suggest that acupuncturists are skilled at gaining and improving therapeutic alliance.

¹ Adler, A. B., Zamorski, M., & Britt, T. W. (2011). The psychology of transition: Adapting to home after deployment. In Adler, A. B., Bliese, P. D., & Castro, C. A. (eds.), *Deployment psychology*. Washington, DC: American Psychological Association.

² Saab PG, et al. ENRICH Investigators. (2009). The impact of cognitive behavioral group training on event-free survival in patients with myocardial infarction: the ENRICH experience. *J Psychosom Res.* 2009 Jul;67(1):45-56. Epub 2009 Apr 1.

³ Cohen, S., et al (1985). Measuring the functional components of social support. In I. G. Sarason & B. R. Sarason (Eds.), *Social support: Theory, research and application* (pp. 73-94). The Hague, The Netherlands: Martinus Nijhoff.

⁴ Cohen, S., et al (1997). Social ties and susceptibility to the common cold. *Journal of the American Medical Association*, 277, 1940-1944